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Hydrazides of glycine-containing decasubstituted pillar[5]arenes: Synthesis and encapsulation of Floxuridine

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ABSTRACT

Hydrazides of glycine-containing decasubstituted pillar[5]arenes were synthesized and characterized. Dynamic light scattering (DLS) and transmission electron microscopy (TEM) showed that self-assembly into monodisperse spherical nanoparticles (28 nm) was typical in water for pillarene hydrazides containing glycylglycide fragments (1×10^{-3} M). Binding of the antitumor drug Floxuridine in water by the substituents of the macrocycle was established by NMR spectroscopy. It was shown by DLS and TEM, that heating the macrocycle-Floxuridine system in a 1:1 ratio at 1×10^{-4} M led to its self-organization into monodisperse spherical particles 132 nm in diameter.

Introduction

The problem of increasing the efficacy of antitumor therapy has recently become acute due to the growth in the number of oncological diseases [1]. Surgical therapy, chemotherapy and immunotherapy are the main methods used in cancer treatment [2a] yet the high toxicity, low bioavailability, poor water solubility, low therapeutic indices, and non-targeted delivery of antitumor drugs to cancer cells remain the main disadvantages of antitumor therapy [2b]. In this regard, the development of new water-soluble molecular capsules capable of increasing the solubility and reducing the toxicity of antitumor drugs is an urgent task for supramolecular chemistry to address [2c]. Supramolecular complexes based on such receptors can be applied to a number of problems related to bioavailability and the targeted action of therapeutic agents [2]. In the last decade [3], several macrocyclic structures have been developed and successfully incorporated in supramolecular drug delivery systems [4]. However, poor aqueous solubility, which significantly narrows the therapeutic window, remains a major problem in the application of macrocyclic hosts [3]. Amphiphilic macrocycles capable of association and aggregation are considered to be the main solution to the above problem [5]. Therefore, we propose to use water-soluble decasubstituted pillar[5]arene derivatives incorporating glycine fragments. It is well known [6] that structural proteins such as elastin and collagen contain a high proportion of glycine residues and that collagen fibrils are components of the intercellular matrix which binds cells in tissues [6b]. In this work, we report the first example of the use of water-soluble pillar[5]arene derivatives containing peptide fragments as self-assembling biomimetic systems [7] for drug delivery.

Previously, we developed a technique [8] to introduce glycine fragments into the pillar[5]arene structure. Macrocycles **3** and **4** were obtained by hydrazinolysis, in 78% and 82% yields, respectively, from decaesters $\mathbf{1}^{8}$ and $\mathbf{2}^{8}$ (ESI S3–S12). Hydrazide fragments were employed as they may allow the target macrocycles to form additional intra- and intermolecular hydrogen bonds [6c]. The polarity of the amide groups and the ability to protonate the terminal amino groups increases the solubility of the substituted macrocycles in water (Fig. 1).

The reactions to obtain macrocycles **3** and **4** were carried out in a 3:1 mixture of methanol/DMF at ambient temperature for 72 h (ESI pp. S3–S12). The self-association of macrocycles **3** and **4** and their aggregation with the antitumor drug 5-Fluorouracil (5-FU) and its derivative 5-fluoro-2′-deoxyuridine (Floxuridine) (FUDR) were studied. These drugs are used to treat colorectal, liver and

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